JACC Vol. 12, No. 2
August 1988:559-69

New York. This work was supported by Grants R01-HL-25055 and K04-HL-01229 from the National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland.

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III. Antagonist's Viewpoint

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In the last several years a number of new nonglycoside positive inotropic agents have been developed for the treatment of patients with congestive heart failure. These new drugs fall into two major categories: the beta-adrenergic agonists and the phosphodiesterase inhibitors (1). Both classes of agents produce marked hemodynamic improvement and appear in clinical practice to exert a substantially greater positive inotropic action than does digitalis. The intravenously administered beta-adrenergic agonists, dopamine and dobutamine, are now widely used in the short-term management of patients with heart failure. In 1978, the initial hemodynamic effects of intravenous amrinone were reported and, subsequently, this agent was approved by the Food and Drug Administration for the short-term management of severe heart failure. Several new second-generation phosphodiesterase inhibitors (such as milrinone, enoximone and piroximone) are available orally on an investigational basis.

Theoretical concerns. The development of potent positive inotropic agents has led to concerns that sustained inotropic stimulation may produce an adverse effect on the survival of patients with congestive heart failure. This concern, initially articulated by Katz (2,3) and subsequently by Packer et al. (4,5), was based on three theoretical fears. First, positive inotropic agents would adversely affect myocardial energetics, thereby hastening the rate of myocardial deterioration. Second, agents that increase myocardial cyclic adenosine monophosphate (AMP) or calcium would provoke complex ventricular arrhythmias, thereby leading to an increase in the incidence of sudden cardiac death. Third, agents that increase myocardial calcium would impair myocardial diastolic relaxation, thereby leading to an increase in diastolic wall stress and cardiac filling pressures.

It is important that these theoretical issues be addressed by prospective, placebo-controlled, double-blind trials. It is particularly imperative that we avoid conclusions based on uncontrolled observations. Although the results of uncontrolled studies may appear to support certain theoretical arguments, other explanations for observed phenomena are usually possible and cannot be excluded in the absence of controlled data. This important point was emphasized by Packer and Leier (5), who noted, "Most of the patients treated with phosphodiesterase inhibitors were severely ill, were deteriorating clinically before therapy and had previously failed vasodilator therapy, often including captopril." These authors concluded that "It is possible that unmeasured variables were present before therapy in patients treated with positive inotropic agents that contributed importantly both to the decision to refer such patients for therapy and to their extremely poor long-term prognosis." Controlled trials are now available, which provide information regarding the effects of long-term positive agents on the clinical status, functional capacity and survival of patients with chronic heart failure.

Effect of beta-adrenergic agonists on survival in heart failure. Attempts to use orally active beta-adrenergic agonists for the treatment of heart failure have not been successful, in large part because tolerance develops to the hemodynamic effects of such agents during long-term therapy (1). Accordingly, patients fail to show persistent hemodynamic and clinical responses to pirbuterol and prenalterol after these orally active beta-adrenergic agonists have been administered for several days (6,7). This hemodynamic attenuation appears to be related to a down-regulation of beta-adrenergic receptors (7) because any prolonged exposure to catecholamines (both experimentally and clinically) results in desensitization of the beta-adrenergic pathway. For example, 5 days of treatment with a beta-adrenergic agonist in the rat results in total loss of the myocardial inotropic responses to pirbuterol and prenalterol, two orally active beta-adrenergic agonists (8).

Because intermittent exposure to catecholamines may circumvent the development of tolerance, intermittent therapy with beta-agonists could conceivably avoid the limitations of continuous treatment. When preliminary data (9,10) suggested that intermittent infusions of dobutamine could favorably affect the clinical status of patients with chronic heart failure, this therapeutic approach was prospectively evaluated in a controlled trial (11,12). Sixty patients with severe chronic heart failure (New York Heart Association functional classes III and IV) were randomly assigned to placebo ($n = 29$) or dobutamine ($n = 31$). After an initial in-hospital evaluation of intravenous dobutamine therapy, patients were discharged home for 24 weeks, where they received an infusion of dobutamine (mean dose 8.1 μg/kg per min) or placebo for 48 h each week by way of an ambulatory, battery-driven infusion pump; 5 days elapsed between each infusion of the drug. Exercise capacity increased more in dobutamine-treated patients than in patients treated with placebo (dobutamine +91%; placebo +13%; $p < 0.05$) (11,12). In addition, clinical deterioration occurred less frequently in the dobutamine-treated group; seven patients were crossed over from placebo to dobutamine because of worsening symptoms of heart failure, whereas only one

patient was crossed over from dobutamine to placebo because of clinical instability ($p < 0.03$).

Of the 37 patients who received dobutamine in this trial (11,12), 15 died (10 suddenly, 4 of progressive heart failure and 1 of sepsis); of these 15 patients, 7 died during the infusion of the drug. Of the 23 patients who were being treated with placebo during their last visit, 5 died (4 suddenly and 1 of progressive heart failure); of these 5 patients, none died during the infusion of placebo. Although the difference in mortality between the two groups was not statistically significant, there was a trend toward a higher mortality in patients treated with dobutamine by both an "intention to treat" ($p = 0.147$) and by an "actual treatment" analysis ($p = 0.06$). Although the latter analysis suggested that dobutamine was associated with an adverse effect on the survival of patients in this study, an "actual treatment" analysis may be misleading because patients whose clinical state was deteriorating were frequently crossed over from placebo to dobutamine. Hence, it is possible that the deaths in this study were related to the therapy that patients were taking when their clinical status began to deteriorate rather than the therapy they were taking when they died. Nonetheless, the findings of this study show a trend toward a higher mortality in patients with chronic heart failure receiving long-term treatment with beta-agonists, a finding that warrants careful consideration.

Effects of dobutamine on sudden death and progression of heart failure. The results of the dobutamine trial permit us to address specific concerns about the long-term effects of positive inotropic agents in chronic congestive heart failure.

Does positive inotropic stimulation lead to a higher incidence of sudden death? Apparently not, because the incidence of sudden death in patients treated with dobutamine (67%) was not higher than that in patients treated with placebo (80%). Does positive inotropic stimulation lead to an accelerated deterioration of cardiac function? Apparently not, because seven of the eight patients whose clinical state deteriorated during the study were being treated with placebo, and exercise capacity improved only in the dobutamine-treated patients. Although myocardial function was not directly measured in this study, these observations suggest that cardiac performance improved (rather than deteriorated) during treatment with dobutamine.

Nearly half (7 of 15) of the deaths that occurred in patients assigned to treatment with dobutamine took place *during* the 48 h weekly infusion of the drug (11,12). This observation suggests that the drug infusion regimen in itself contributed importantly to the high mortality seen in treated patients. If deaths occurring during the infusion of dobutamine are excluded from the analysis, the mortality in the two treatment groups is similar (8 [22%] of 37 for dobutamine; 5 of 23 or 22% for placebo). In this study, a relatively high dose (mean dose 8.1 μg/kg per min) of a potent agent was administered to patients whose metabolic status and arrhythmia prevalence were not known before or during the infusion. The study design did not permit physicians to detect or correct potential metabolic and electrolyte abnormalities or to treat any electrical complications that might have occurred. Hence, conclusions regarding the effect of positive inotropic drugs on the survival of patients with chronic heart failure are not warranted on the basis of findings of the intermittent intravenous dobutamine trial.

Effect of phosphodiesterase inhibitors on survival in heart failure. The first phosphodiesterase inhibitor to be evaluated in a controlled clinical trial was amrinone (13). This agent, when administered to 99 patients with moderate to severe heart failure for 3 months, appeared to have no effect on survival when compared with placebo. Unfortunately, we can draw few conclusions from this study because dose-related side effects necessitated either the withdrawal of or a reduction in the dose of amrinone to subtherapeutic levels in the majority of patients. The use of low doses of the drug probably explains the inability of this trial to demonstrate any benefit of amrinone on symptoms and exercise tolerance. Several new phosphodiesterase inhibitors exhibit a more favorable toxic/therapeutic ratio than does amrinone and therefore appear more likely to be clinically useful during long-term therapy.

To date, most of the reported long-term experience with phosphodiesterase inhibitors has been with milrinone, a second-generation congener of amrinone that is hemodynamically effective during long-term therapy (1). Three recently completed trials (referred to as P-706, P-712 and M1-1A) have evaluated the long-term efficacy and safety of milrinone in patients with chronic heart failure.

Trial P-706 (14,15) enrolled 230 patients with moderate to severe symptoms with a mean left ventricular ejection fraction of 0.23. After patients were clinically stable on a regimen of digitalis and diuretics for 4 to 8 weeks, they were randomly assigned (in a double-blind manner) to one of four treatment groups for 3 months: diuretics alone (digoxin withdrawal), diuretics plus digoxin, diuretics plus milrinone (substitution of milrinone for digoxin) or diuretics plus both digoxin and milrinone (addition of milrinone to previous regimen). Crossover from placebo to active drug groups was not allowed. In patients withdrawn from digoxin, milrinone produced a significant increase in exercise capacity compared with placebo (14,15). Twenty-one of the 230 patients died during the 3 month trial. Multivariate analysis indicated that only the pretreatment left ventricular ejection fraction was a significant predictor of survival in this study. Unfortunately, the randomization process resulted in a significant imbalance in the values for ejection fraction in the four treatment groups such that more patients with a very low ejection fraction were randomly assigned to treatment with milrinone ($p < 0.01$). When the survival of patients in this study was adjusted for this imbalance, there was no significant effect of milrinone on mortality, regardless of the

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method of analysis ("intention to treat", p = 0.26 or "actual treatment", p = 0.34).

A second trial (P-712) enrolled 155 patients with moderate to severe chronic heart failure. After stabilization on treatment with digitalis and diuretics, patients were randomly assigned (in a double-blind fashion) to one of three treatment groups for 3 months: diuretic plus digoxin, diuretic plus milrinone (substitution of milrinone for digoxin) and diuretic plus digoxin and milrinone (addition of milrinone to previous regimen). In this trial, the randomization process resulted in a similar distribution of values for left ventricular ejection fraction among the treatment groups, and thus no adjustment of survival data was required. As in P-706, no effect of milrinone on survival was found (p = 0.87) (15).

A third trial (M1-1A) enrolled 186 patients with moderate to severe chronic heart failure who were randomly assigned to treatment with either milrinone or placebo for 6 months in addition to their previous therapy with digoxin and diuretics. As in P-706 and P-712, milrinone had no effect on survival (p = 0.75) (15).

These three controlled trials (reflecting the experience with milrinone in 571 patients) do not support the thesis that long-term treatment with positive inotropic drugs adversely affects survival in chronic heart failure. However, these findings should not be generalized to other positive inotropic agents, including other phosphodiesterase inhibitors, because other drugs may differ from milrinone in significant ways.

Effects of milrinone on sudden death, myocardial energetics and diastolic relaxation. Do the data for milrinone (2-5) support any of the theoretical mechanisms by which positive inotropic agents may adversely affect survival in chronic heart failure? *Does milrinone increase the incidence of sudden death?* Apparently not. In studies P-706 and P-712, the incidence of sudden death with milrinone (40%) was similar to that seen in patients who received placebo (45%) (14,15). In trial M1-1A, the incidence of sudden death with milrinone (50%) was no greater than that for placebo (100%) (15). These data do not support the thesis that positive inotropic agents adversely affect the incidence of sudden death in chronic heart failure.

Does milrinone exert an adverse effect on myocardial energetics in chronic heart failure? Because myocardial contractility is an important determinant of myocardial energy expenditure, it is possible that positive inotropic agents may increase myocardial oxygen consumption and thereby adversely affect energy stores in the failing heart. The improvement in pump function that follows milrinone therapy, however, is not associated with an increase in myocardial oxygen demand (16,17), presumably because the peripheral vasodilating effects of milrinone act to reduce myocardial oxygen consumption and thus offset any adverse effect on myocardial energetics that might be expected to follow an increase in cardiac contractility.

Finally, does milrinone adversely affect myocardial relaxation (lusitropy) or diastolic filling in chronic heart failure? Apparently not. Both intravenous and oral milrinone have been shown to improve diastolic function, as evidenced by a downward displacement of the left ventricular diastolic pressure-volume relation that follows treatment with this drug (18,19). Hence, milrinone appears to exert a favorable direct lusitropic action, as might be anticipated after the administration of any agent that acts to increase myocardial levels of cyclic adenosine monophosphate (AMP).

Effects of milrinone on survival in experimental heart failure. The rat coronary artery ligation model of left ventricular dysfunction has been used to demonstrate that both captopril (20) and enalapril (21) improve survival in experimentally induced chronic heart failure. Recently, Sweet et al. (21), using the same model, demonstrated that milrinone increased the median survival time of rats with myocardial infarction by 49%; the magnitude of this benefit exceeded that seen with enalapril in the same model. Although such data cannot be extrapolated to the clinical setting, they do not support the view that positive inotropic agents adversely affect survival and they raise the possibility that milrinone could affect survival in a beneficial way.

Conclusions. Controlled data with milrinone do not demonstrate an adverse effect of long-term treatment with this drug on the survival of patients with chronic heart failure, and they fail to support the importance of any of the theorized mechanisms by which positive inotropic agents could potentially adversely affect survival. Although these data are encouraging, final conclusions regarding the effects of positive inotropic agents on patient survival will require larger studies conducted for longer periods of time. Because the extent to which the safety profile of milrinone is favorably influenced by the drug's peripheral vasodilator actions is unknown, these data do not allow conclusions regarding the safety of pure positive inotropic agents. Preliminary observations with the intermittent use of intravenous dobutamine in chronic heart failure do not allow conclusions regarding the long-term effects of positive inotropic therapy but raise concerns regarding the safety of the ambulatory dobutamine infusion method.

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